A STUDY ON INFLAMMATORY BOWEL DISEASE AND THE ROLE OF SEROLOGICAL MARKERS

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CERTIFICATE

This is to certify that this dissertation entitled **"STUDY ON INFLAMMATORY BOWEL DISEASE AND ROLE OF SEROLOGICAL MARKERS** by **Dr.A.Chezhian** to the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance.

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CONTENTS

INTRODUCTION

Inflammatory bowel disease is one of the chronic debilitating illnesses and is a challenge to the treating gastroenterologist and to the patient. The most common form of inflammatory bowel disease in India is ulcerative colitis[1].During 1960's all the cases of chronic bloody diarrheas were diagnosed as amebic colitis or infective colitis. Tandon and chuttani et al first described ulcerative colitis in india[2]. There are lots of articles published from south India also cites its increasing incidence [3-5.]

The incidence of ulcerative colitis varies from 1.2 to 20 per 100,000 person-years and its prevalence from 40 to 246 per 100,000 persons in studies conducted across the world [6.]

Ulcerative colitis begins in rectal mucosa circumferentially and spreads to involve the proximal portions continuously without any skip areas. The inflammation involves mucosa and submucosa and no transmural involvement which is a feature of crohns disease. There are lots of diseases that can mimic ulcerative colitis from the commonly occurring infections to the rare forms of atypical colitis.

There is no single test to diagnose ulcerative colitis available now. The diagnosis of ulcerative colitis is based on a combination of clinical, endoscopic and histopathological findings. We have to rule out some infections and atypical colitis before making a diagnosis of ulcerative colitis. But still there is lots of confusion regarding the ultimate confirmation of the diagnosis before starting the therapy. Sometimes colonoscopy is not tolerated by the patients especially in acute setup. We need newer tools to make diagnosis.

Inflammatory bowel diseases (IBD) are subdivided into ulcerative colitis (UC) and Crohn's disease (CD). Several lines of evidence suggest that CD and UC are different diseases. However, some patients (10–12%) cannot be easily classified into either and a final diagnosis of indeterminate colitis is made. Making an earlier, more accurate diagnosis of IBD is important as the management of CD and UC is different, especially when surgery is planned[7,8].

A search for serological tests to differentiate CD from UC has been underway for a long time[7]. An ideal serological marker should have high sensitivity, high specificity, and high predictive values[9,10].

So in this study I want to assess the usefulness of serological markers as a diagnostic test and correlation with other parameters in the natural history of ulcerative colitis and there are already lots of studies available regarding this in western literature but lacking in south India especially using panel of markers.

REVIEW OF LITERATURE

Inflammatory bowel disease is a chronic inflammatory disease of predominantly small and large intestine. Crohn's disease and ulcerative colitis are the two main types. There are other less common entities like atypical microscopic colitis, primary Collagenous colitis and lymphocytic colitis. Although in many ways similar the diversion colitis, bypass enteropathy, radiation colitis and drug induced colitis have various identifiable etiologies[14].

Ulcerative colitis is first described by Dr.Samuel Wilks in 1859 and he described this as Idiopathic colitis and thought this disease is different from bacillary dysentery[15]. Tandon and chuttani et al first described ulcerative colitis in India [2].

Epidemiology:

The most common form of inflammatory bowel disease in India is ulcerative colitis[1]. The incidence of ulcerative colitis varies from 1.2 to 20 per 100,000 person-years and its prevalence from 40 to 246 per 100,000 persons in studies conducted across the world [6]

This disease is said to be more common in northern part of the world. Ulcerative colitis is more common in Jews population. But it may

present in all age groups with peak in second or third decade. Patients as young as 5 years can be affected. It is very rare beyond 8th decade. There is no predilection for any sex and male: female ratio is said to be 1:1[16.]

More common in industrialized areas. Urban population, high socioeconomic status, immigrants to high risk areas are the other associations which are well documented[17,18].

Etiopathogenesis:

The disease is said to be due to the complex interplay of genetic, environmental, immunological and psycho logical factors. But the exact etiology is not known.

Evidence for genetic factors are best demonstrated in twins studies. Also there are lots of case reports in which parent son or siblings involved are reported. Another point is younger age of onset in familial form[19] .There are more than one gene involvement and following genes are more commonly reported.MDR1 gene,HLA-DR2, DR1 and sometimes DR3 also[20,21].

Environmental also involved in the pathogenesis as the studies conducted in immigrants. Infections are strongly suspected especially mycobacterium[24]. Involvement of intestinal micro flora also is postulated.

Cigarette smoking is another strong negative predictor[22]. Patients who quits smoking, mild smoker than heavy smoker, passive than active are at higher risk.

Dietary factors responsible are wheat, maize, cow's milk, OC pills, refined sugar, alcohol, fruits, vegetables, toothpaste and breastfeeding, but none has been proved. Appendicectomy is a negative risk factor [22,23].

Immune mechanisms are also postulated. Both humoral and cell mediated immunity plays a role. Both the systems were deregulated [25,26]. The best described autoantibody is pANCA. This autoantibody is present in 60 to 85% of ulcerative colitis patients. Most found evidence is in favor of its role as a susceptibility marker in first degree relatives of patients with ulcerative colitis. Regarding the cellular immunity both T cell mediated and nonspecific immunity also is implicated[27,28].

Psychogenic factors also are postulated but later found to be associations due to the disease rather than cause of it[29].

Pathology:

Ulcerative colitis is a disease that starts from rectum and progressing proximally. It always involves the mucosa circumferentially. It involves mucosa and submucosa but not transmurally into serosa.

Continuous and symmetrical involvement is the hallmark of the disease. But there are some exceptions to this rule as in those treated with enemas will have rectal sparing. 75% of patients with left sided colitis have appendiceal involvement[30].

Endoscopy :

Common sites of involvement

rectosigmoid -45%

left sided - 35%

pancolitis - 20%

This is as per western data and this correlates with Indian data[5,6].

Macroscopic appearance:

Mucosa is hyperemic, edematous and granular in mild cases. In severe cases hemorrhagic mucosa with punctuate ulcers. The ulcers enlarge and extends into submucosa. They are irregular with overhanging edges. linear ulcers along the line of the taenia coli is also occurs. Due to recurrent attacks and subsequent regeneration of the mucosa, pseudopolyp formation occurs. In long standing cases the mucosa is atrophic and futureless resulting in shortening and narrowing of the

intestine occurs. Finally with severe disease the colon dilated and the mucosa becomes thinner and grossly ulcerated. Sometimes perforates with fibrinopurulent exudation [31].

Microscopic appearance:

During active disease

1) lamina propria edema
2) congestion of capillaries and venule
3) Extravasation of RBC's
4) acute inflammatory cell infiltration
5) cryptitis and crypt abscess
6) goblet cell mucin depletion

During healing phase

1) inflammatory cells clears
2) epithelial regeneration
3) Regenerating epithelia mimics dysplastic cells.

During chronic phase

1) Distortion of crypts

2) Branching bifid glands

3) Paneth cell metaplasia

4) Crypt atrophy

5) <6 crypts per 1mm [32]

CLINICAL FEATURES:

Rectal bleeding

Proctitis- fresh blood streaked on stool mistaken for hemorrhoids

Left sided UC- blood mixed with stool

Severe UC - Anchovy sauce stool (pus, blood & mucus)

Absence of rectal bleed rules out active UC

Diarrhea

In 70% patients

30 % may have constipation

Tenesmus,

Nocturnal diarrhea

Abdominal pain :

Rare symptom

Vague pain usually

Miscellaneous :

Fever

Edema, weight loss

Fatigue

Anorexia and vomiting.

Signs:

Abdomen tender

Velvety mucosa in rectum

Fever,

Tachycardia,

Weight loss,

Clubbing,

Edema,

Hypoalbuminemia

Extraintestinal manifestations:

Extraintestinal manifestations can affect any organ system, but they most commonly involve the skin, eyes, mouth, joints, and liver. These complications often are classified by their relations to the activity of the

colitis, but they can occur before, during, or following exacerbations of bowel disease[33,34].

Cutaneous/Oral

Angular stomatitis

Aphthous stomatitis

Erythema nodosum

Oral ulcerations

Psoriasis

Pyoderma gangrenosum

Pyostomatitis vegetans

Sweet's syndrome (acute febrile Neutrophilic dermatosis)

Ophthalmologic

Conjunctivitis

Episcleritis

Retinal vascular disease

Scleritis

Uveitis, iritis

Musculoskeletal

Ankylosing spondylitis

Osteomalacia

Osteonecrosis

Osteopenia

Osteoporosis

Peripheral arthropathy

Sacroiliitis

Hepatobiliary

Autoimmune hepatitis

Cholangiocarcinoma

Pericholangitis

Primary sclerosing cholangitis

Hepatic steatosis

Hematological

Anemia of chronic disease

Autoimmune hemolytic anemia

Iron deficiency anemia

Hypercoagulable state

Leukocytosis or thrombocytosis

Leucopenia or thrombocytopenia

CUTANEOUS/ORAL

The most common dermatologic manifestations of UC are complications of drug treatment. These include hypersensitivity, photosensitivity, and urticarial rashes related to sulfasalazine and less commonly to mesalamine. Patients receiving glucocorticoids often develop acne, which can be distressing cosmetically. Other common dermatologic manifestations associated with UC are erythema nodosum and pyoderma gangrenosum.

At least 10% of patients with UC develop oral aphthous ulcers. These lesions usually occur with flares of colitis and resolve on control of the bowel disease. Angular stomatitis and a sore tongue may be seen in patients with deficiencies of iron, B vitamins, or other micronutrients . A rare oral lesion that may be seen in patients with UC is pyostomatitis (pyoderma) vegetans, which appears as a pustular eruption of the oral mucosa resulting in a cobblestone appearance.

OPHTHALMOLOGIC

The two most common ocular manifestations associated with UC are episcleritis and uveitis, occurring in 5% to 8% of patients. Episcleritis is characterized by painless hyperemia of the sclera and conjunctiva without loss of vision. It typically parallels the activity of bowel disease and usually responds to anti-inflammatory therapy.

Peripheral Arthropathy

Peripheral arthropathy occurs in 5% to 20% of patients with UC. The risk of arthropathy increases with the extent of colonic disease. Peripheral arthropathy can be classified into two distinct types[36].

Peripheral Arthropathy Associated with Ulcerative Colitis

FEATURE	TYPE1 (PAUCIARTICULAR)	TYPE2 (POLYARTICULAR)
Characteristics		
Frequency	35%	24%
Duration of attacks	<10 wk (median, 5 wk)	Months to years (median, 3 yr)
Association with bowel disease activity	Parallel	Independent
Joints Affected		
Number	<5	≥5
Type	Mainly large joints	Mainly small joints
Prevalence	Knee > ankle > wrist > elbow > MCP > hip > shoulder	MCP > knee > PIP > wrist > ankle > elbow > shoulder

Hepatobiliary

The most important hepatobiliary complication associated with UC is PSC, which occurs in approximately 3% of patients (see Chapter 68). PSC is a chronic inflammatory disease of the biliary tree resulting in fibrosis and, eventually, cirrhosis and hepatic failure. Intrahepatic or extrahepatic ducts (or both) may be involved.

Miscellaneous:

Secondary systemic amyloidosis is a rare but serious complication associated with UC. Amyloidosis in these patients usually affects the kidney and manifests with proteinuria followed by the nephrotic syndrome and subsequent renal insufficiency. Diagnosis is made with a fat pad aspiration or alternatively, biopsies from the liver, rectum, or kidney. Pericarditis, pleuropericarditis, and constrictive pericarditis have been reported in patients with UC .This complication also may be related to mesalamine therapy. The pathogenesis of these complications is unknown, and their true association with UC is uncertain. Patients with UC can also develop abnormalities in pulmonary function, including an increase in functional reserve capacity and a decrease in diffusion capacity. Other pulmonary diseases that have been described in patients with UC include bronchiectasis, bronchiolitis, fibrosing alveolitis, pulmonary fibrosis, and pulmonary vasculitis.

Diagnosis:

There is no single test that allows the diagnosis of UC with acceptable sensitivity and specificity. Diagnosis relies on a combination of compatible clinical features, endoscopic appearances, and histologic findings. The diagnosis of UC should be questioned if there is only a

single episode of acute illness or if the histopathology findings are nonspecific and lack signs of chronicity[35].

Endoscopy:

In patients presenting with their first attack of UC, sigmoidoscopy with biopsies usually is sufficient to confirm the diagnosis, thereby allowing initiation of therapy. In patients with active flares, sigmoidoscopy is best performed in unprepared bowel so the earliest signs of UC can be detected. Multiple biopsy specimens should be taken from throughout the colon to map the histologic extent of disease and to confirm the diagnosis[36].

The hallmark of UC is symmetrical and continuous inflammation that begins in the rectum and extends proximally without interruption for the entire extent of disease. The earliest endoscopic sign of UC is a decrease or loss of the normal vascular pattern, with mucosal erythema and edema. As disease progresses, the mucosa becomes granular and friable. With more-severe inflammation, the mucosa may be covered by yellow-brown mucopurulent exudates associated with mucosal ulcerations.Mucosal ulcerations occur in areas of inflammation, vary in size from a few millimeters to several centimeters, and may be punctate, annular, linear, or serpiginous. Finally, severe UC is associated with

mucosa that bleeds spontaneously, and, with diffuse colitis, there may be extensive areas of denuded mucosa from severe mucosal ulcerations. Marked edema can at times lead to narrowing of the lumen.

In patients with long-standing UC, pseudopolyps may be present. Inflammatory pseudopolyps develop in active disease and result from inflamed, regenerating epithelium that is interposed among ulcerations,may give the colonic mucosa a cobble stoned appearance. Endoscopically, pseudopolyps typically are small, soft, pale, fleshy, and glistening;[36]

There is a loss of normal colonic architecture with long-standing inflammation that is characterized by muscular hypertrophy, loss of the normal haustral fold pattern, decreased luminal diameter, and shortening of the colon; a resultant featureless appearance of the colon in chronic UC gives rise to the lead pipe appearance seen on barium enema. Strictures can occur. Malignancy must be excluded in patients with long strictures without associated inflammation and strictures proximal to the splenic flexure.

RADIOLOGY:

In the presence of severe disease, the luminal margin of the colon—the interface between the colonic mucosa and the luminal gas—becomes edematous and irregular. Thickening of the colonic wall often is apparent on a plain film. The presence of marked colonic dilatation suggests fulminant colitis or toxic megacolon. A plain abdominal film also can detect unsuspected free air[37].

The earliest radiologic change of UC seen on barium studies is fine mucosal granularity. The mucosal line becomes irregular and is not as sharp as that of a normal colon. With increasing severity, the mucosal line becomes thickened and irregular, and superficial ulcers are well shown en face. Deep ulceration can appear as collar-stud or collar-button ulcers in tangent, which indicates that the ulceration has extended through the mucosa to the muscularis propria.

Inflammatory and noninflammatory diseases of the colon can mimic UC and need to be considered in establishing the correct diagnosis. This differential diagnosis can be grouped broadly into three categories: Crohn's disease, infections, and noninfectious causes.

Serological markers in IBD:

Perinuclear antineutrophil cytoplasmic autoantibodies (pANCA) are a well recognised marker for ulcerative colitis[38]. Antibodies to oligomannosidic epitopes of the yeast *Saccharomyces cerevisiae* (ASCA) are a marker associated with Crohn's disease [39].

The combination of a positive pANCA test and a negative ASCA testyielded a sensitivity, specificity, and positivepredictive value of 57%, 97%, and 92.5% respectively for ulcerative colitis[40].

The combination of a positive ASCA test and a negative pANCA test yielded a sensitivity, specificity, and positive predictive value of 49%, 97%, and 96% respectively for Crohn's disease[41-43].

A search for serological tests to differentiate CD from UC has been underway for a long time. An ideal serological marker should have high sensitivity, high specificity, and high predictive values[44].

The prevalence of pANCA varies from 40% to 80% in UC and from 0% to 20% in CD[45]. Testing for the presence of anti-*S cerevisiae* mannan antibodies (designated ASCA) was 64% sensitive and 77% specific for discriminating CD from UC and 89% specific for distinguishing CD from controls.

Differential Diagnosis of Ulcerative Colitis:

Microscopic colitis

Ischemic colitis

Infectious colitis

Amebic colitis

Pseudomembranous colitis

Endoscopic Differentiation of Ulcerative Colitis and Crohn's Disease

FEATURE	ULCERATIVE COLITIS	CROHN'S DISEASE
Distribution	Diffuse inflammation that extends proximally from the anorectal junction	Rectal sparing, frequent skip lesions
Inflammation	Diffuse erythema, early loss of vascular markings with mucosal granularity or friability	Focal and asymmetrical, cobblestoning; granularity and friability less commonly
Ulceration	Small ulcers in a diffusely inflamed mucosa; deep, ragged ulcers in severe disease	Aphthoid ulcers, linear or serpiginous ulceration; intervening mucosa is often normal
Colonic lumen	Often narrowed in long-standing chronic disease; tubular colon; strictures are rare	Strictures are common

ASSESSMENT OF DISEASE ACTIVITY

Assessment of disease activity is important for prognostication and therapeutic decision making. Although none of these indices is accepted universally as standard, one of the most commonly used is that of Truelove and Witts. This purely clinical classification categorizes disease as mild, moderate, or severe based on a combination of clinical findings and laboratory parameters, including frequency of bowel movements, rectal bleeding, fever, tachycardia, anemia, and elevated ESR. The Truelove and Witts classification is reliable and simple to use in clinical practice, although it is most applicable for patients with extensive colitis and might not adequately reflect disease severity in patients with limited colitis.

Truelove and Witts Classification[46]

Mild

<4 stools/day, without or with only small amounts of blood

No fever

No tachycardia

Mild anemia

ESR < 30 mm/hr

Severe

>6 stools/day, with blood

Fever > 37.5?C

Heart rate > 90 beats/min

Anemia with hemoglobin level < 75% of normal

ESR > 30 mm/hr

A numerical disease activity instrument that is more useful for patients with limited disease and for conducting clinical trials is the Ulcerative Colitis Disease Activity Index (UCDAI, also known as the Sutherland Index). his index, which combines clinical and endoscopic assessments, is the sum of scores from four components: stool frequency, rectal bleeding, sigmoidoscopic findings, and physician's global assessment. This disease activity index ranges from 0 to 12, with the higher total scores representing more-severe disease. In general, a patient

is considered to be in remission if the UCDAI score is 2 or less and to have severe disease if the score is greater than 10. Clinical response generally is accepted to be reflected by a decrease of three points from the patient's initial baseline score. An index very similar to the UCDAI that has been used extensively in recent randomized, controlled trials (RCTs) is the Mayo score, which incorporates the same four components as the UCDAI.

Other scales also have been developed, many of which are modifications of the Truelove and Witts classification and the UCDAI. None of these disease activity instruments has ever been formally validated. There also exist many endoscopic and histologic scales for grading the severity of colitis . Endoscopic findings do not always correlate with clinical symptoms, and such correlations generally are more consistent within individuals. Thus, although therapeutic decisions are based primarily on clinical status, it may be useful to follow the sigmoidoscopic mucosal appearance over time in an individual patient, if the clinical response to treatment is uncertain.

Endoscopic Assessment of Disease Activity in Ulcerative Colitis

Endoscopic Assessment

Grade 0	Normal mucosa
Grade 1	Loss of vascular pattern
Grade 2	Granular, nonfriable mucosa
Grade 3	Friability on rubbing
Grade 4	Spontaneous bleeding, ulceration

In addition to the typical categorization of disease activity into mild, moderate, and severe, an important subgroup is fulminant colitis. Patients with severe colitis who appear toxic, with fever higher than 38.3 C (101 F), tachycardia, abdominal distention, signs of localized or generalized peritonitis, and leukocytosis, are considered to have Fulminant colitis. Toxic mega colon is said to occur when there is radiologic evidence of transverse colon dilatation to greater than 6 cm in an acutely ill patient. Fulminant colitis and toxic megacolon are clinical diagnoses, and complete colonoscopy examination should be avoided in patients with severe or Fulminant colitis because of the risk of inducing mega colon or perforation. In this patient population, a limited flexible Sigmoidoscopy is appropriate to ensure that the etiology of the symptoms is UC itself and not other conditions[47,48].

TREATMENT

MEDICAL

The goals of therapy of UC are

To induce remission,

To maintain remission,

To maintain adequate nutrition,

To minimize disease- and treatment-related complications.

Aminosalicylates

Oral

Sulfasalazine consists of an antibacterial component, sulfapyridine, bonded by an azo bond to a salicylate, 5-aminosalicylic acid (5-ASA, mesalamine) (The drug was synthesized by Nana Svartz in 1938-1939 and its benefit for the treatment of IBD was discovered serendipitously in 1941-1942 by her when patients with UC receiving this medication for a presumed diagnosis of rheumatoid arthritis noted improvement in colitis symptoms . 5-ASA is the principal therapeutic moiety of sulfasalazine in IBD and that the sulfapyridine component of the parent drug serves as an inactive carrier, largely preventing absorption of 5-ASA in the small intestine and allowing it to be released in the colon[49]. Approximately 90% of sulfasalazine reaches the colon, and only a small amount is absorbed in the small intestine. On reaching the colon, the enzyme azoreductase,

which is elaborated by colonic bacteria, cleaves the azo bond to release the active constituent moiety, 5-ASA. After 5-ASA is absorbed from the colon, 20% of the compound undergoes hepatic acetylation, forming *N*-acetyl 5-ASA, and is excreted in the urine. Sulfasalazine is one of several agents in the class of 5-ASA compounds that is considered to be the first line of therapy for inducing remission in patients with mild to moderate UC. Mesalamine derivatives have not been evaluated in a randomized, controlled fashion in patients with severely active disease. At a dose of 3 to 6 g/day, sulfasalazine induces remission in 39% to 62% of patients with mild to moderate UC[50,51].

Various formulations and controlled-release systems have been developed to deliver 5-ASA to specific sites of the gastrointestinal tract without the sulfapyridine moiety, which is thought to be responsible for most of the side effects. Olsalazine is a 5-ASA dimer linked by an azo bond and is formulated in gelatin capsules. Balsalazide consists of a 5-ASA monomer linked to a biologically inactive carrier molecule, 4-aminobenzoyl-β-alanine. Similar to sulfasalazine, 5-ASA is released from olsalazine and balsalazide in the colon upon cleavage of the azo bond via the bacterial enzyme azoreductase. Approximately 99% of the drug is delivered intact to the colon, and its metabolites are cleared rapidly in the urine[52].

Oral 5-Aminosalicylic Acid Preparations and Sites of Delivery in the Gastrointestinal Tract

DRUG	FORMULATION	SITE OF DELIVERY
Prodrugs		
Sulfasalazine	Sulfapyridine + 5-ASA	Colon
Olsalazine	5-ASA dimer	Colon
Balsalazide	4-aminobenzoyl β-alanine + 5-ASA	Colon
Mesalamine Preparations		
Asacol, Claversal, Salofalk	pH sensitive, resin-coated; delayed release	Distal ileum, colon
Rowasa	Enema	Distal colon
Canasa	Suppository	Rectum
Pentasa	Ethylcellulose-coated microgranules; controlled release	Duodenum to colon
Lialda	pH sensitive, multi-matrix and polymethacrylate coated; delayed and slow release	Distal ileum, colon

Three commonly used mesalamine preparations allow delivery of 5-ASA before the drug reaches the colon: Pentasa, Asacol, and Lialda. Pentasa uses ethyl cellulose-coated microgranules that release mesalamine from the duodenum throughout the small bowel and the

colon; about 50% of 5-ASA is released in the small intestine, and the remainder is released in the colon. Asacol is a Eudragit-S-100–coated mesalamine tablet that is released at a pH greater than 7, usually in the distal ileum and the colon. With Asacol, about 15% to 30% of mesalamine is released in the small intestine. Lialda (MMx mesalamine) is a novel mesalamine formulation that uses a multimatrix structure composed of an inner lipophilic matrix and an outer hydrophilic matrix. It is coated with a pH-dependent polymethacrylate film to allow the delayed release of mesalamine in the terminal ileum and colon at a pH greater than 7. This technology also allows mesalamine to be released slowly and in close proximity to the colonic mucosa.

More important than the specific 5-ASA preparation is the dose-dependent response when 5-ASA is used as an induction therapy for active UC. For this indication, mesalamine is not effective at doses lower than 2 g daily, and there is an increased response at doses of 4 to 4.8 g daily. The ASCEND I and II trials showed that mesalamine at doses of 2.4 and 4.8 g/day have similar efficacy for patients with mildly active disease, but the higher dose (4.8 g/day) was more efficacious in patients with moderately active disease. This dose of mesalamine is comparable to 12 g/day of sulfasalazine, which is impractical in clinical practice because of the high probability of intolerance. No RCT has evaluated the use of

aminosalicylates for severely active UC, but these agents are generally thought not to be effective in severely active disease.

Glucocorticoids

Systemic

At doses equivalent to 40 to 60 mg/day of oral prednisone, glucocorticoids are effective first-line therapy for moderate or severe flares of UC.] The use of doses higher than 60 mg/day is associated with increased side effects without appreciable clinical benefit and thus should be avoided. The addition of sulfasalazine to corticosteroids in moderately to severely active UC does not offer any incremental benefit. Although no study has directly compared the efficacy of oral and parenteral glucocorticoids, the latter commonly are used in severe disease. No adequately designed controlled study has been performed to confirm the clinical impression that continuous infusion of parenteral glucocorticoids is superior to pulse therapy.

Immunomodulators

Azathioprine and 6-Mercaptopurine

Of the various immunomodulatory agents, the most widely used are azathioprine and 6-MP. These two agents are purine analogs that

interfere with nucleic acid metabolism and cell growth and exert cytotoxic effects on lymphoid cells. They are inactive prodrugs with subtle structural differences. Azathioprine is nonenzymatically converted to 6-MP, which is then metabolized through a series of enzymatic pathways to active and inactive metabolites . The two primary metabolites of 6-MP are 6-thioguanine nucleotides (6-TGNs) and 6-methylmercaptopurine (6-MMP). The 6-TGN metabolites are thought be responsible for the immunomodulatory action of azathioprine and 6-MP and their bone marrow suppression property, whereas hepatotoxicity is thought to be related to 6-MMP. One key enzyme involved in the biotransformation of 6-MP is thiopurine methyltransferase (TPMT), which converts 6-MP to its inactive metabolites, 6-MMP and 6-methylmercaptopurine ribonucleotides[53].

Biological Therapy

Recent advances in our understanding of the pathogenesis of IBD have resulted in the development of therapies targeted at specific molecules or mediators involved in the inflammatory processes of these diseases. Most studies evaluating the efficacy of these agents have been performed in patients with Crohn's disease, and only limited data are available for patients with UC[55].

Anti-Tumor Necrosis Factor Antibodies

TNF is a key proinflammatory cytokine that has been demonstrated to play a role in several disease states, including IBD. Elevated TNF concentrations have been found in inflamed intestine in patients with Crohn's disease and UC, and stool and mucosal concentrations of TNF in patients with IBD have been shown to correlate with clinical disease activity. Infliximab is a chimeric monoclonal antibody of IgG_1 subclass directed against human TNF-α. It consists of 75% human and 25% murine components [55] . The efficacy of infliximab in Crohn's disease is well established, and it is approved by the FDA to treat Crohn's disease and UC. Infliximab is thought to operate in Crohn's disease via a multitude of mechanisms, including antagonizing the activity of TNF-α, initiating cytotoxicity on immune cells, and inducing T-cell apoptosis.

Results from two large, multicenter, randomized, double-blind, placebo-controlled trials (ACT 1 and 2) showed efficacy of infliximab therapy in UC. In these two similarly designed trials, 728 patients with moderately to severely active UC who failed conventional therapy with glucocorticoids alone or in combination with thiopurines (ACT 1) or glucocorticoids alone or in combination with thiopurines and 5-aminosalicylates (ACT 2) were randomized to placebo, infliximab

5 mg/kg, or infliximab 10 mg/kg at weeks 0 and 2 and then every eight weeks through week 46 (ACT 1) or week 22 (ACT 2). With respect to clinical response at week 8, in ACT 1 69% and 61% of patients receiving infliximab at 5 and 10 mg/kg, respectively, had a clinical response, compared with 37% of patients receiving placebo ($P < 0.001$ for both comparisons). In ACT 2 at week 8, 64% and 69% of patients receiving infliximab at 5 mg/kg and 10 mg/kg, respectively, had a clinical response, compared with 29% of patients receiving placebo ($P < 0.001$ for both comparisons). With respect to clinical remission at week 8 in ACT 1, 39% and 32% of patients receiving infliximab at 5 mg/kg and 10 mg/kg, respectively, attained remission, compared with 15% of patients receiving placebo ($P < 0.003$ for both comparisons). In ACT 2 at week 8, 34% and 28% of patients receiving infliximab at 5 mg/kg and 10 mg/kg, respectively, attained remission, compared with 6% of patients receiving placebo ($P < 0.001$ for both comparisons). The results for clinical remission at week 30 (ACT 1 and 2) and week 54 (ACT 1) were very similar for all groups, with highly significant greater than two-fold higher remission rates for the infliximab-treated patients. The proportions of patients with a sustained clinical response or remission also were significantly higher in the infliximab groups. Treatment with infliximab also was shown to have steroid-sparing and mucosal healing properties[55].

These data have led to the approval of infliximab by the FDA for patients with moderately to severely active UC who have had an inadequate response to conventional therapy. Infliximab is now accepted as part of the standard treatment options in patients with UC. Two other anti-TNF agents, adalimumab and certolizumab pegol, have shown efficacy for the induction and maintenance of remission in Crohn's disease but have not yet been studied in patients with UC[56].

Anti-Adhesion Molecules

Several agents directed at blocking small adhesion molecules have been evaluated for the treatment of UC. These molecules are glycoproteins expressed on the surfaces of endothelial cells and lymphocytes. Adhesion molecules are important in cellular trafficking in IBD and other diseases, in which immune and inflammatory cells from the periphery are recruited into sites of inflammation. Among these, natalizumab is a humanized IgG_4 monoclonal antibody against lymphocyte adhesion molecules, α_4 integrins. A pilot study of 10 patients with active UC suggested clinical benefit with a single infusion of 3 mg/kg of natalizumab.Natalizumab currently is approved for treating patients who have Crohn's disease and in whom anti-TNF therapy has failed; its use in UC is now undergoing evaluation[57].

Another anti-adhesion molecule agent is MLN-02 (formerly called *LDP-02*), a humanized IgG_1 monoclonal antibody to $\alpha_4\beta_7$ integrin. In a phase 2 study, two infusions of 0.5 mg/kg of MNL-02 administered 29 days apart were found to be effective in achieving clinical remission and response at six weeks after the initial infusion in patients with moderately active UC.

Others

Although historically considered more important in the inflammation of Crohn's disease, as it is produced by Th1 cells, IL-2 also has been implicated in UC inflammation (see earlier). Two agents designed to block the binding of IL-2 to its receptor have been examined for potential efficacy in UC. Daclizumab, a humanized monoclonal antibody against the IL-2 receptor (CD25), was suggested to be beneficial in patients with refractory UC in a small open-label pilot study. A potential clinical benefit also has been reported with basiliximab, a chimeric monoclonal antibody to the IL-2 receptor, in a small, uncontrolled study of patients with steroid-refractory UC. Along with the emphasis on T-cell–mediated immune response in the pathogenesis of UC, a humanized monoclonal antibody to CD3, visilizumab, has shown

promise in an open-label phase 1 study of 32 hospitalized patients with UC whose disease failed to respond to intravenous glucocorticoids [58].

Other biological therapies include agents targeted at tissue repair and restitution following mucosal injury. In this regard, epidermal growth factor (EGF) is a potent mitogenic peptide that stimulates cell proliferation in the gastrointestinal tract. A preliminary study showed that EGF enemas at a dose of 5 ?g daily for two weeks was effective in treating mild to moderate left-sided UC when administered along with oral mesalamine. In contrast, another potent stimulant of intestinal epithelial cells, repifermin (keratinocyte growth factor 2) was not found to be more effective than placebo when administered intravenously in patients with active UC in a phase 2 dose-ranging study. Further studies clearly are necessary to confirm some of these early promising findings[59,60].

Cytapheresis

Active UC is characterized by activation and infiltration of leukocytes in the colonic mucosa. Because leukocyte-derived inflammatory cytokines play an important role in initiating and perpetuating the inflammatory process, reduction of peripheral blood

levels of leukocytes has been proposed as a therapeutic option for treating UC.

Surgery:

Indications for Surgery in Patients with Ulcerative Colitis

Colonic dysplasia or carcinoma

Colonic hemorrhage, uncontrollable

Colonic perforation

Growth retardation

Intolerable or unacceptable side effects of medical therapy

Medically refractory disease

Systemic complications that are recurrent or unmanageable

Toxic megacolon

Proctocolectomy with Ileal Pouch-Anal Anastomosis

Restorative proctocolectomy with IPAA currently is the operation of choice for most patients with UC who require elective colectomy. In this procedure, the entire colon and rectum are removed, the anal sphincters are preserved, and a pouch is constructed from approximately 20 cm of the distal ileum . Bowel continuity is established by anastomosing this pouch with the anal canal. An IPAA usually is

performed as a two-stage operation, during the first stage of which a temporary diverting ileostomy is created to allow the ileal pouch to heal[61].

Complications:

- Toxic megacolon
- Strictures
- Dysplasia and colorectal cancer
- Pouchitis[62]

Prognosis:

Despite the burden of a chronic illness, more than 90% of patients with UC are able to maintain capacity for work after 10 years of disease, and data suggest that the overall quality of life is not impaired significantly, including marital issues, physical activities, and social function. The disease can affect the quality of life to some degree during acute flares, however, and even during periods of remission, patients might remain anxious for fear of relapse and alter their lifestyle accordingly.

Despite the morbidity of UC, mortality associated with the disease has dropped dramatically since the late 1950s and 1960s. The mortality

rate for a severe attack of UC was approximately 35% before the introduction of glucocorticoid therapy and now is less than 2%. Long-term survival does not differ significantly from that expected for age-matched controls, even with the risk of colorectal cancer that attends long-standing colitis. It is now generally believed that patients with UC have life expectancies comparable to those of the general population, although studies have reached conflicting conclusions. Mortality risk is greatest in the elderly and in those with extensive colitis, mostly related to postoperative complications within the first two years of disease and to comorbidities[63].

AIM OF THE STUDY

1. To study the environmental and psychosocial factors associated with ulcerative colitis.

2. To study the clinical presentations, natural history and extraintestinal manifestations of ulcerative colitis.

3. To study the usefulness of panel of serological markers in the diagnosis of ulcerative colitis.

4. To study any correlation of serological markers with clinical presentation, disease severity and natural course of the disease.

5. To study the effects of therapy on serological markers and any correlation with poor response to therapy.

MATERIALS AND METHODS

This is a prospective study conducted in Department of digestive health and diseases, Government peripheral hospital, Annanagar, Chennai-102 from April 2009 to March 2011. The following inclusion and exclusion criteria were followed.

Inclusion criteria:

Patients with clinical endoscopic, histological features suggestive of Ulcerative colitis.

Exclusion criteria:

1. Patients with nonspecific colitis
2. Patients with infective colitis
3. Patients with radiation colitis
4. Patients with diversion colitis
5. Patients with features of ulcerative colitis but biopsy indeterminate.

First the study protocol was designed and our institutional ethical committee approved the design of the study. Then the patients included in the study were explained about the entire study and informed consent was obtained.

All the patients who attended our OPD during the study period with symptoms of chronic diarrhea were included in our study. Those patients were informed about the colonoscopy procedure and consent obtained for colonoscopy.

All the patients prepared with PEGLEC preparation as per routine protocol of our hospital. We usually instruct the patients to be on liquid diet 24 hours prior to colonoscopy. One packet of PEGLEC mixed with 2 liters of plain water and the patient were asked to drink it in the previous day evening. Two tablets of bisacodyl also were prescribed for patients with hard stools in the previous day night. Patient were not allowed anything by mouth from 10 pm onwards. Patients were given intravenous fluid if required.

Colonoscopy was done either with IV sedation or without any anesthesia in the morning. Colonoscopy was done by using PENTAX videocolonoscope. Biopsies were taken as required and sent to our pathologist for tissue diagnosis.

Diagnosis of Ulcerative colitis was made by combination of clinical features, endoscopic appearance and histopathological examinations.. They are investigated completely to diagnose ulcerative

colitis. Only histopathologically confirmed cases from our hospital during the study period were included in this study.

All the particulars of the patients were obtained as per proforma attached herewith it. Patients were interviewed about their demographic details first. Then detailed history about clinical presentation, natural history, past, personal, family histories, environmental and psychological factors prior to the onset of the disease were asked. Also extraintestinal manifestations were notified.

Complete hemogram, basic blood chemistry, liver function tests and other routine investigations were done as per proforma. For serological markers 3 ml of blood taken separately and all the serological markers as mentioned in the proforma were done by indirect immunoflourescent assay. Serological markers done are

1. Antibody to goblet cells-IgA and G

2. p ANCA IgA and G

3 c ANCA IgA and G

4 Antibody to pancreatic antigen IgA and G

5 Antibody to pancreatic acini IgA and G

6. ANA

ANCA INDIRECT IMMUNOFLUORESCENCE ASSAY

Determination of pANCA was performed by an indirect immunofluorescence technique on ethanol fixed leucocytes according to the International guidelines on ANCA. Fluorescein isothiocyanate conjugated rabbit antihuman IgG (specific for ã chains) (Dako, Glostrup, Denmark) was used. Patient sera were screened at a dilution of 1/20 in phosphate buffered saline. All slides were assessed by two well trained observers in a blinded fashion.

ASCA ASSAY:

ASCA ELISA Antigen consisted of phosphopeptidomannan (PPM) extracted from yeast cells from cultures in bioreactors. ELISA was performed as previously described. Briefly, plates were coated with 100 µl of PPM at a concentration of 1 µg/ml in sodium carbonate buffer (60 mM, Ph 9.6), for one hour at 37°C and overnight at

4°C, in moist chambers, and then washed four times in TNT (50 mM Tris-HCl, 150 mM NaCl, 0.05% Tween 20, pH 7.5). Patient sera were diluted 1/1000 in TNT and tested in duplicate. Alkaline phosphatase labelled goat antihuman immunoglobulin (IgG, IgA, IgM;H and L chains; Zymed, Biosoft, Paris, France) was diluted 1/3000 in TNT. A colour

reaction was obtained by using substrate Biotrol EIA 405 (Biotrol, Paris, France) for alkaline phosphatase.The plates were read at 405 nm on an Immunotech (Luminy, France) automatic reader. A coefficient of variation of less than 2% corresponded to repeatability of optical density values on a single microtitre plate. Interseries reproducibility of ASCA values showed a coefficient of variation of less than 5%. In a previous study it is described the standardisation procedure which was designed to avoid variations in individual values observed between series of the immunological assay. Each set of experiments involved six dilutions of the standard (1/500–1/32 000) from which a standard curve was derived. The highest absorbance (saturation) observed at 405 nm, was arbitrarily defined as 100% reactivity. Results of individual sera were expressed as a relative reactivity extrapolated from the standard curve and calculated by the ELIOT program (Immunotech, Luminy, France)..This was then used to determine the threshold of the test (3.12%). Serological markers were compared among various groups ie. pan colitis Vs limited colitis, new patients Vs treated patients, those with extraintestinal manifestations and those without and also its usefulness as a diagnostic marker alone or in combinations.

First the usefulness of individual serological markers to diagnose disease was analyzed. At one side patients were separated into pan

colitis group and limited colitis group and various serological markers were analyzed. Then patients separated based on new cases and patients already on sulphasalazine therapy and serological markers were analyzed. Both the above groups were demographically matched. Also patients were analyzed based on presence or absence of extraintestinal manifestations and its correlation with serological methods.

Statistical methods:

When studying the relation between test results and clinical parameters, the chi square test or Fisher's exact test was used when appropriate, and a multivariate analysis was performed using a logistic regression model. Significance was assigned to any probability value less than 0.05.

The statistical software package SPSS for windows version [SPSS Inc, Chicago III] was used to analyze the data. means and standard deviations were used to summarize data for continuous variables whereas percentages were used for categorical variables.

Definition : Multiple extra intestinal involvement means > 2 systems involved

Suphasalazine Response means patients on maintenance with sulphasalazine for > 2 years without increase in symptoms and or relapses controlled with sulphasalazine.

RESULTS

In this study period 11543 patients attended our OPD as new cases. Out of which 398 colonoscopies were performed during this period for varying indications .Out of which 120 cases chronic diarrhea cases were analysed. Among this 51 patients were having features suggestive of IBD endoscopically.11 patients were excluded from final analysis. Among those excluded are 7 patients for having not turned up for follow up and 4 patients had inconclusive histopathological results. Among this 40 cases of histopathologically proven cases of ulcerative colitis were finally included in this study.

Table : study particulars

Serial Number :	Factors	Numbers
1	Total OPD	11543
2	Total colonoscopy	398
3	Chronic diarrhea	120
4	Endoscopically IBD	51
5	Patients excluded	11
6	Total included in study	40

Among the 40 patients 20 patients were male and 20 patients were females. From 15 years to70 years is the age range .Patients mean age in this study is 42.5 years. Peak onset is in the 3rd or 4th decade. All the patients were from low socioeconomic group and geographic region is around north Tamilnadu as it reflects the location of our hospital.

Table 1. Demographic details:

Factors	Numbers
Male/female	1:1
Age range	15 to 70 years
Mean age	42.5 years
Commonest age group	3rd or 4th decade[19/40]

Table 2. Risk factors :

S:no	Risk factors	present	absent	Cumulative %	P value
1	Smoking	22	18	55	0.52
2	Alcohol	6	34	15	
3	Tea	34	6	85	.00
4	Unpasteurised milk	28	12	70	.011
5	Appendicectomy	0	40	-	
6	Breast feeding	36	4	90	
7	OC pills	0	20	-	
8	Chronic mental stress	28	12	70	.011

All the known risk factors given in literature were analyzed using questionnaire. One patient had history of pulmonary tuberculosis. Majority were from urban areas and north Tamilnadu. Majority patients are Hindus by religion and poor socioeconomic status. But all these epidemiological data reflects are local factors.

None of the patients have family history of IBD. Ulcerative colitis is more common among smokers in this study(55% vs 45%) but only 15% of study population is consuming alcohol. Only 15% of the study

population is not breastfed. None of the patients underwent appendicectomy a mong the females none were using contraceptive pills. But 8o% of the study population used to drink lots of tea [p value .00] and 70 % of patients found to be using either unpasteurised milk or raw milk [p value 01]. most importantly 70 % of patients were suffered persistent mental agony long prior to the onset of IBD[P value .01].

While analyzing the symptoms rectal bleeding and chronic diarrheas were more common and found in 90 %. of the patients. Abdominal pain is present in 70% of the patients. Fatigue and edema legs were found in 35%, 20% respectively. 31 of the patients were having chronic relapsing course[78% vs 22%] and only 9 patients has chronic continuous course . 33 patients were showing good response to sulphasalazine[83%]. Sulphasalazine related adverse events were rare and found only in 4 patients [10% p value .00].

Table 3. clinical features

Serial no :	symptom	present	absent	Cumulative %	P value
1	Rectal bleed	36	4	90	.00
2	Chronic diarrhea	36	4	90	.00
3	Abdominal pain	28	12	70	.00
4	fatigue	14	26	35	.58
5	Edema legs	8	32	20	.00
6	Chronic relapsing course	31		77.5	
7	Chronic continuous course	9		22.5	
8	Response to sulphasalazine	33	7	82.5	
9	Sulphasalazine adverse events	4	36	10	.00

The onset of the illness has no seasonal preference. The mean duration of symptoms before the diagnosis of the disease is 7 months.

Table 4. Extraintestinal manifestations

Serial no	System abnormalities	present	absent	Cumulative%	P value
1	dermatologic	14	26	35	.58
2	rheumatic	34	6	85	.00
3	ophthalmologic	26	14	65	.58
4	hepatobiliary	0	40	-	
5	pulmonary	12	28	30	.011

Extraintestinal manifestations are more commonly found in this study. Dermatologic manifestations were found in 35% of the patients. Rheumatic manifestations are found in 85 % of the patient s. Ophthalmologic manifestations in 65%,and 30% patients had pulmonary manifestations. But characteristic hepatobiliary manifestations are not found in any of our patients. Pancreatic ,urologic and hematologic manifestations also are not found in the study population. But regarding extraintestinal manifestations patients need to be followed for longer period to know the true incidence.

Table 5. Prevalence of serological Markers

Serial no:	Serological marker	positive	negative	Cumulative %
1	Anti goblet cell antibody	5	35	12.5
2	P ANCA	27	13	67.5
3	ASCA	4	36	10
4	Anti pancreatic antigen antibody	0	40	-
5	ANA	15	25	37.5

Panel of serologic markers were done in the study population. Anti goblet cell antibodies were positive in 12.5%, p ANCA in 67.5%, ASCA in 10 % and ANA in 37.5%. antibody to pancreatic antibody is negative in all patients.

Table 6. Disease extent and serological markers

S. No.	Serolo-gical marker	Pancolitis		Cumula tive %	P val-ue	Limited colitis		%
		Positive	negative			Posi-tive	negative	
1	Anti goblet cell ab	4	16	20	.15	1	19	5
2	P ANCA	20	0	100	.00	7	13	35
3	ASCA	1	19	5	.29	3	17	15
4	Anti pan. antibody	0	20			0	20	
5	ANA	10	10	50	.10	5	15	25

In the cross analysis of patients with severe UC and serological markers, patients with pancolitis are having 100 % positive for p ANCA[P<.OO] , 50% ANA,20 % antigoblet cell antibody and only 5% positivity for ASCA. At the same time patients with limited colitis has only 35 % positivity for p ANCA

Table 7. Serological markers in treatment naive patients

S. No.	Serological marker	Treatment naïve		Positive %	P value	On treatment		Positive %
		pos	neg			pos	neg	
1	Anti goblet cell antibody	3	17	15	.63	2	18	10
2	P ANCA	16	4	80	.09	11	9	67.5
3	ASCA	1	19	5	.29	3	17	15
4	ANA	8	12	40	.74	7	13	37.5

Then we compared the two groups of treatment naïve and on treatment with panel of serological markers. There is a marked difference in p ANCA levels between treatment naïve and on treatment groups[80% vs 67.5 p value<.09] but this is statistically not significant.

When comparing the patients with more extraintestinal involvement with those of less involvement indicates value of p ANCA. The pANCA is positive in those with severe extraintestinal involvement compared to other group[94 % vs 47% p value <.02].ANA also useful eventhough it is statistically not significant[60% vs 26 % p <.08] .Antigoblet cell antibody has significant negative correlation with multiple extraintestinal involvement.

Table 8. Serological markers and multiple extraintestinal involvement

S. No.	Serological marker	Severe involve-ment		Positive %	P value	Mild involvement		Positive %
		pos	neg			pos	neg	
1	Anti goblet cell antibody	4	13	23.5	.07	1	22	4.3
2	P ANCA	16	1	94	.02	11	12	47.8
3	ASCA	1	16	5.9	.45	3	20	13
5	ANA	9	8	60	.08	6	17	26

Table 9. Serological markers and sulphasalazine response

Serial no:	Serological marker	Good response		Positive %	P value	Poor response		Positive %
		pos	neg			pos	neg	
1	Anti goblet cell antibody	2	31	6	.008	3	4	43
2	P ANCA	20	13	61	.04	7	0	100
3	ASCA	4	29	12	.33	0	7	
5	ANA	10	23	30	.04	5	2	33

Although p ANCA is found to be elevated in both groups antigoblet cell antibody negativity predicts poor response to sulphasalazine[p value <.008]

Table 10. Serological markers and natural course of UC

Serial no:	Serological marker	Chronic relapsing		Positive %	P value	Chronic continuous		Positive %
		pos	neg			pos	neg	
1	Anti goblet cell antibody	5	26	16	.19	0	9	0
2	P ANCA	21	10	68	.95	6	3	66
3	ASCA	3	28	10	.90	1	8	11
4	ANA	10	21	32	.20	5	4	33

The role of serum markers in predicting the natural course of illness is not well defined but antigoblet cell antibodies is 100 % negative in patients who are going for a chronic continuous course.

DISCUSSION

Among the 40 patients 20 patients were male and 20 patients were females. From 15 years to70 years is the age range .Patients mean age in this study is 42.5 years. Peak onset is in the 3rd or 4th decade as noted in the literature[Tandon et al]. All the patients were from low socioeconomic group, Hindus by religion, from urban areas and geographic region is around North Tamilnadu as it reflects the location of our hospital .this epidemiological features correlates with the available literature.

In the present study we analyzed the genetic, environmental and psychological factors in the study population. The significant findings noted are consumption of raw or unpasteurized milk in 70% [p value of 0.011]. Then regular consumption of tea as the beverage is found in 85% [p value of 0.00].

The presence of chronic persistent mental stress is found in 70%[p value of 0.011] as noted in the literature. But the other risk factors such as lack of breastfeeding, use of OC pills are not significantly identified in our study. None of the study population had appendicectomy [Rutgeerts P, D'Haens] and only one patient had pulmonary tuberculosis in the past. Contrary to literature the majority of the study population are smokers

[55%] either active or passive[D Jones et al]. No family history of UC was found in our study.

In the present study we analysed the clinical features and rectal bleeding and chronic diarrhea were the most common symptoms and is found in 90 % of the study population. Abdominal pain is present in 70% of the patients. Fatigue and edema legs were found in 35%, 20% respectively. And this clinical pattern correlates with available literature.

In this study 31 of the patients were having chronic relapsing course[78% vs 22%] and only 9 patients has chronic continuous course **.** 33 patients were showing good response to sulphasalazine[83%]. We found Sulphasalazine as a cheaper drug and more useful. In this study sulphasalazine related adverse events were rare and found only in 4 patients [10% p value .00]. the mean duration of symptoms before diagnosis was made is 7 months which is as reported in literature.

In this study rheumatic manifestations are found in 85 % of the patients. Ophthalmologic manifestations in 65% but others are rare. one of our actually presented first with unrelenting arthritis and started on NSAID ,then she subsequently started manifesting colonic symptoms. Surprisingly pulmonary symptoms were found in 30 % of the patients.

None of the hepatobiliary manifestations were found in this study which is contrary to the available literature[Thayumanavan et al].

In the present study, we assessed the prevalence of ASCA pANCA, anti goblet cell antibodies and ANA in a small population of ulcerative colitis and their value in differentiating between pancolitis and limited colitis, correlation with histopathology for diagnostic sensitivity and specificity, sulphasalazine response and no response, presence or absence of multiple extraintestinal manifestations and prediction of natural course.

At present, it appears that ASCA and pANCA are strongly associated with CD and UC, respectively. Our percentages of serum samples from patients with UC which were pANCA positive[67.5%] and ASCA positive [10%] are comparable to the data reported in literature[**Ferrante M et al].** But antigoblet cell antibodies are positive in only [12.5%] patients.

In our study population of 20 patients with pancolitis all showed p ANCA positivity[p .00]. The presence of pANCA in UC was dependent of disease extent which is contrary to available literature. Although statistically not significant ASCA is more positive [15 %] in patients with limited colitis than pancolitis[5%]

Increasing evidence supports the concept of clinical and genetic heterogeneity in IBD and serum immune markers have been used to characterize subgroups of patients. pANCA were also present in patients who had been on treatment for longer periods confirming previous reports. [**Severine et al] .** But p ANCA is found to be more positive in treatment naïve[80%] than on treatment group[67.5%] with a p value of 0.09 **[Dubinsky MC et al].**

In the present study, the presence of p ANCA could be associated with particular clinical features in the form of more extraintestinal manifestations [94% ,p value of 0.02] which is not supported by existing literature., thus confirming our previous report. However, to confirm whether ANCA represent a serological marker of a clinical severity we need further studies.

In the present study p ANCA was positive in [61%] sulphasalazine responders and when combine with antigoblet antibody negativity[94%] it significantly correlates with sulphasalazine response p=0.004.**Behera et al** described elevation of ANA in steroid dependant patients. However the serological markers does not predicts the natural course of the disease. But antigoblet cell antibodies were found to be negative in all the patients who is running a chronic continuous course in this study.

However, since variation in prevalence of serological markers, such as pANCA, have been observed worldwide, it is recommended that multicentre, prospective studies be conducted.

CONCLUSION

1. Positive p ANCA along with negative ASCA can be used as an additional diagnostic marker in ulcerative colitis.

2. Positive p ANCA along with negative ASCA is a marker of disease extent.

3. Positive p ANCA along with negative antigoblet cell antibodies can predict poor response to drug therapy.

4. Positive p ANCA can predict multiple extraintestinal system involvement warrants longterm followup.

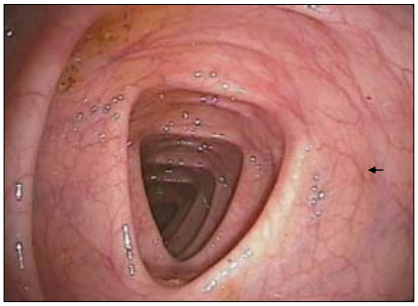
5. Positive p ANCA along with negative antigoblet cell antibodies can predict chronic continuous course of ulcerative colitis.

6. Extraintestinal manifestations are common and rheumatologic manifestations were the most common of it.

7. Psychological factors have a definitive precipitating role in ulcerative colitis.

Normal Splenic Flexure

Colonoscopic view of normal splenic flexure with haustral folds and normal vascular pattern.



Normal Transverse Colon

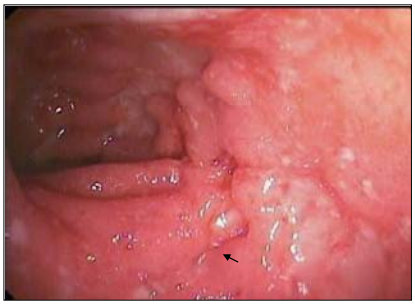
This endoscopic image depicts colon showing haustral folds with normal vascular pattern.

Mild Ulcerative Colitis

Colonoscopic view showing patchy loss of vascular pattern friability and few erosions covered by white exudate.

Ulcerative Colitis: Mayo Score 2

Colonoscopic view showing loss of vascular pattern friability and fine ulceration.



Ulcerative Colitis: Mayo Score 3

Colonoscopic view showing extensive ulcerations, friability and loss of vascular pattern.

PROFORMA

Name : Age : Sex : DD
HD No.

Residence : Occupation :
Mobile No.:

EPIDEMIOLOGICAL		PAST HISTORY	
North / South		DM	
Ethnicity		SHT	
Religion		CAHD	
Urban / Rural		PTB	
Socio Economic Status		SD	
		BA	
FAMILY HISTORY		JAUNDICE	
		ABD-SURGERY	
		APPENDICECTOMY	
		ANY OTHER	
PERSONAL HISTORY		**DIET HISTORY**	
Smoker		Rice : Boiled / Raw	
Heavy		Wheat / Maize	
Moderate		Milk - Type	
Mild		Sugar – Refined	
Ex.		Fruits or Vegetables	
Passive		OC Pills	
Alcohol Abuse		Toothpaste	

Tobacco		Breast Fed / or Not	
Betel nut / Betel Lime		Non Veg. Foods	
Carbonated Drinks		Any other	
CLINICAL		**EXTRA INTESTINAL**	
On set to Diagnosis		Rheumatic A (+) or (-)	
On set < Stress Seasons		H/o Swollen joint in the past / present H/o. Reduced Physical activity	
Rectal Bleeding		H/o Morning stiffness	
Diarrhea		H/o Low Back pain at rest / improve with activity	
Constipation		H/o Restricted spine / hand movement	
Abdominal Pain		O/E Clubbing	
Anorexia / Wt. Loss / Nausea / Vomiting		Joint swelling : Sym / Pauci / Poly / Mig.	
Fever		**METABOLIC : A (+) OR (-)**	
Fatigue		H/o Fractures, Hip, Back	
Peripheral Edema		H/o Generalized Bone Pain	
Other Symptoms		H/o Muscle weakness	
COURSE :		H/o Hypocalcemia	
.One attach only		O/E Waddling gait	
Fulminant		**HBP A (+) OR (-)**	
Chronic Continuous		H/o Jaundice	
Chronic Intermittent		H/o Cholangitis	
Any other		H/o RUQ Pain	
DERMATOLOGIC A (+) or (-)		H/o Pancreatic Pain	

Erythema Nodosum		**UROLOGICAL A (+) OR (-)**	
Pyoderma Gangrenosum		H/o Renal Colic	
Sweet Syndrome		**PULMONARY A (+) OR (-)**	
Apthous ulcers		H/o Chronic Productive cough	
Any other		H/o Wheeze / Dyspnea / Hemoptysis	
		RS	
OPHTHALMOLOGIC A (+) OR (-)		**SULPHA SALAZINE USERS :**	
H/o Painful eye		Anorexia / Nausea / Vomiting	
H/o Blurred vision		Head ache / Back ache	
H/o Photophobia		Alopecia	
H/o Irritation		H/o Colitis	
H/o Burning eye		H/o Chest pain	
O/E Miosis		H/o Cough / Wheeze / Dyspnea	
Abnormal Pupillary res.		H/o Jaundice	
Ciliary Flush		H/o Pancreatic Pain	
Tenderness Eye		H/o Fever	
Redness between vessels		H/o Arthralgia	
Hyperemic vessels		H/o Infertility	
Violet Eye		Any other	
Slit Lamp Examination		**CIBD PROFILE**	
ENDOSCOPY		Ab to Goblet cells – IgA and IgG	
Rectosigmoid		PANCA IgA and IgA	
Leftsided		Ab to DNA bound Lactoferrin IgG	
Pancolitis		Ab to Pancreatic Antigen rPAg1 IgA/G	

Ileal Disease		Ab to Pancretic Antigen rPAg2 IgA/G	
Perianal Disease		Ab to Pancreatic Acini IgA and IgG	
Grading		ASCA IgA and IgG	
LABORATORY PARAMETERS :		**SERUM**	
Stool – OVA / CYST		Calcium	
Urine – Albumin / Sugar		Phosphorus	
Deposits / RBC		Vitamin D	
BLOOD		PTH	
Hb%		**HOMOCYSTINE**	
TC		CRP	
DC		**LIPID PROFILE : TGL**	
ESR		LDL / VLDL	
RBC count		HDL	
BT / CT		Total Cholesterol	
Platelet count		HBS Ag	
Peripheral Smear		Anti HCV Ab	
RBC Parameters		X-rays : Chest	
Blood Urea / Sugar / Cre		Others	
Serum Na + / K+ / Cl- / HCO3-			

LIVER FUNCTION TEST				
TB / DB		**USG ABDOMEN**		
OT		MRCP		
PT		ERCP		
SAP		CECT		
TP		DEXA		
ALB / GLO		ECG In all leads		
Serum Amylase		HPE		

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MASTER CHART - 1

No	Sex	Severity	/Old	Int.	Response	Course	Goblet	ANCA	ASCA	Pan	ANA
1	52/F	1	2	1	1	1	2	1	2	2	1
2	30/F	1	1	1	1	1	2	1	2	2	2
3	24/F	2	2	2	1	2	2	2	2	2	2
4	36/F	1	2	2	1	1	2	1	2	2	2
5	57/M	1	1	1	2	1	1	1	2	2	2
6	60/F	2	1	1	1	2	2	1	2	2	2
7	37/M	1	2	1	2	2	2	1	2	2	1
8	38/M	1	2	1	1	1	1	1	2	2	1
9	30/M	2	1	2	1	1	2	2	1	2	2
10	47/M	2	2	2	1	1	2	1	2	2	2
11	45/M	1	2	2	1	1	2	1	2	2	2
12	45/M	2	2	2	1	3	2	2	2	2	2
13	40/M	1	1	2	1	1	2	1	2	2	1
14	55/F	2	2	2	1	1	1	2	2	2	1
15	37/M	2	2	2	1	1	2	2	1	2	2
16	45/M	2	2	2	1	1	2	2	1	2	2
17	28/F	1	1	2		2	2	1	2	2	1
18	25/F	1	1	2	2	1	2	1	2	2	1
19	65/F	1	1	2	1	1	2	1	2	2	2
20	42/M	2	1	2	1	1	2	1	2	2	1

No	Sex	Severity	/Old	Int.	Response	Course	Goblet	ANCA	ASCA	Pan	ANA
21	62/F	1	1	1	2	1	1	1	2	2	1
22	24/F	2	1	2	1	1	2	2	2	2	2
23	54/M	2	1	2	1	1	2	2	2	2	2
24	40/F	1	1	1	2	1	1	1	2	2	2
25	53/M	1	1	1	1	1	2	1	2	2	2
26	70/M	2	1	1	1	1	2	1	2	2	1
27	32/F	1	2	1	1	1	2	1	2	2	2
28	24/M	1	1	1	1	1	2	1	2	2	1
29	50/M	2	1	1	1	1	2	1	2	2	2
30	37/F	2	1	2	1	1	2	2	2	2	2
31	54/F	2	1	1	1	1	2	1	2	2	1
32	56/M	2	2	2	1	1	2	2	2	2	2
33	46/M	2	2	2	1	1	2	2	2	2	2
34	38/M	1	1	2	1	1	2	1	2	2	2
35	48/M	1	2	1	2	2	2	1	2	2	1
36	35/M	2	2	2	1	1	2	1	2	2	2
37	65/F	2	2	1	1	2	2	2	2	2	1
38	22/F	2	2	2	1	1	2	2	2	2	2
39	45/F	1	2	1	1	2	2	1	1	2	2
40	15/F	1	2	2	1	2	2	1	2	2	1

MASTER CHART - 2

S.No	Age & Sex	On set to Diagnosis	Smoking	Alcohol	Tea	Un Past. Milk	Appendi Cectomy	Breast Feeding	OC Pill	Chronic Mental Stress	Rectal Bleeding	Chronic Diarrhea	Abdominal Pain	Edema	Fatigue	Derm	Rheu	Opthal	HPB	Pul
1	52/F	7 Months	1	2	1	1	2	1	2	1	1	1	1	2	1	1	1	1	2	2
2	30/F	1 Month	2	2	2	1	2	1	2	1	2	2	1	2	1	1	2	1	2	2
3	24/F	2 Years	1	2	1	2	2	2	2	2	1	1	2	2	1	1	1	2	2	2
4	36/F	1 Month	2	2	1	1	2	1	2	1	1	1	1	2	2	2	2	2	2	2
5	57/M	3 Months	1	1	1	2	2	1	2	1	1	1	1	2	1	1	1	1	2	2
6	60/F	3 Months	1	2	1	1	2	1	2	1	2	2	1	2	2	1	1	1	2	2
7	37/M	1 Year	1	2	1	1	2	1	2	2	1	1	2	2	2	1	1	2	2	2
8	38/M	2 Years	1	1	2	1	2	1	2	2	1	1	1	2	1	2	1	1	2	1
9	30/M	9 Months	2	1	1	2	2	1	2	2	1	1	1	2	1	1	1	1	2	1
10	47/M	4 Months	2	2	1	2	2	1	2	1	1	1	1	2	2	2	1	2	2	1
11	45/M	6 Months	1	2	1	1	2	1	2	1	1	1	1	2	2	2	2	1	2	1
12	45/M	8 Months	1	2	1	1	2	1	2	1	1	1	1	2	2	2	1	2	2	2
13	40/M	8 Months	1	2	1	1	2	1	2	1	1	1	1	2	1	2	1	1	2	1
14	55/F	9 Months	2	2	1	1	2	1	2	1	1	1	1	1	2	2	1	2	2	2
15	37/M	6 Months	2	2	1	2	2	1	2	1	1	1	2	1	2	2	1	1	2	1
16	45/M	9 Months	1	2	2	1	2	2	2	1	1	1	2	1	2	2	1	1	2	1
17	28/F	7 Months	2	2	1	2	2	1	2	1	1	1	2	1	2	2	1	1	2	2
18	25/F	8 Months	2	2	1	1	2	1	2	1	1	1	1	2	2	2	1	1	2	1
19	65/F	1 Month	1	2	1	1	2	1	2	2	1	1	1	2	2	2	1	1	2	2
20	42/M	1 Month	2	2	1	1	2	1	2	2	1	1	2	2	2	2	1	2	2	2
21	62/F	7 Months	1	2	1	1	2	1	2	1	1	1	1	2	1	1	1	1	2	2

S.No	Age & Sex	On set to Diagnosis	Smoking	Alcohol	Tea	Un Past. Milk	Appendi Cectomy	Breast Feeding	OC Pill	Chronic Mental Stress	Rectal Bleeding	Chronic Diarrhea	Abdominal Pain	Edema	Fatigue	Derm	Rheu	Opthal	HPB	Pul
22	24/F	1 Month	2	2	2	1	2	1	2	1	2	2	1	2	1	1	2	1	2	2
23	54/M	2 Years	1	2	1	2	2	2	2	2	1	1	2	2	1	1	1	2	2	2
24	40/F	1 Month	2	2	1	1	2	1	2	1	1	1	1	2	2	2	2	2	2	2
25	53/M	3 Months	1	1	1	2	2	1	2	1	1	1	1	2	1	1	1	1	2	2
26	70/M	3 Months	1	2	1	1	2	1	2	1	2	2	1	2	2	1	1	1	2	2
27	32/F	1 Year	1	2	1	1	2	1	2	2	1	1	2	2	2	1	1	2	2	2
28	24/M	2 Years	1	1	2	1	2	1	2	2	1	1	1	2	1	2	1	1	2	2
29	50/M	9 Months	2	1	1	2	2	1	2	2	1	1	1	2	1	1	1	1	2	1
30	37/F	4 Months	2	2	1	2	2	1	2	1	1	1	1	2	2	2	1	2	2	1
31	54/F	6 Months	1	2	1	1	2	1	2	1	1	1	1	2	2	2	2	1	2	1
32	56/M	8 Months	1	2	1	1	2	1	2	1	1	1	1	2	2	2	1	2	2	1
33	46/M	8 Months	1	2	1	1	2	1	2	1	1	1	1	2	1	2	1	1	2	2
34	38/M	9 Months	2	2	1	1	2	1	2	1	1	1	1	1	2	2	1	2	2	2
35	48/M	6 Months	2	2	1	2	2	1	2	1	1	1	2	1	2	2	1	1	2	2
36	35/M	9 Months	1	2	2	1	2	2	2	1	1	1	2	1	2	2	1	1	2	2
37	65/F	7 Months	2	2	1	2	2	1	2	1	1	1	2	1	2	2	1	1	2	2
38	22/F	8 Months	2	2	1	1	2	1	2	1	1	1	1	2	2	2	1	1	2	2
39	45/F	1 Month	1	2	1	1	2	1	2	2	1	1	1	2	2	2	1	1	2	2
40	15/F	1 Month	2	2	1	1	2	1	2	2	1	1	2	2	2	2	1	2	2	2